Applicants respectfully petition, pursuant to 37 C.F.R. 1.17(a) and 1.136(a), a three-month extension of time, i.e., up to and including June 5, 2001. Enclosed herewith is a check for $890.00 in payment of the fee thereof. Any deficiency or overpayment in this fee, or any other fee occasioned by this paper or any overpayment in any other fee occasioned by this paper may be charged or credited to Deposit Account No. 50-0320.

Applicants wish to thank the Examiner for withdrawing the objections to the specification and the rejection of claim 1 under 35 U.S.C. § 101, in light of the amendments filed on September 5, 2000.

Claims 2 to 9 and 16 are pending in this application.

Claims 2 to 9 and 16 were rejected in the Office Action under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete and for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. (Office Action, pages 3 to 5).

In view of the following remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, because the claims include all of the necessary steps for one skilled in the art to practice the invention as claimed and the language of the claims clearly define the invention.

This invention relates to a combinatorial process for preparing chemical compounds of the following chemical scaffold

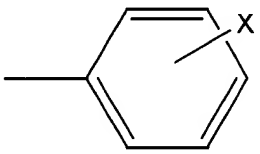
$$Y\text{-}R^1\text{-}P(=O)(\text{-}O\text{-}R^3)(\text{-}R^2)$$

upon which diverse chemical compounds can be made. Compounds possessing this chemical scaffold are known in the art to be useful in human or veterinary medicine and in plant protection. This invention also provides for some novel intermediate compounds which possess

the phosphorus containing backbone and relate specifically to solid-phase based chemical processing.

The claimed process is defined through the use of generic formulae (II), (IV), (IV)',(V), (V)', (VI), (VI)', (VII), (VII)', (VIII), (VIII)' and (IX), and includes a definition for the "linker" group and the connection of the linker, Z, E^1 and S^1 groups to one another. These formulae define the chemical structures of compounds developed when practicing the claimed process in terms of generic formulae that would be utilized by one skilled in the art of combinatorial chemistry. These formulae do not define all of the potential chemical bonds in a limited manner, however, they do define the invention in terms that would be clear to one skilled in the art seeking to practice the claimed invention.

For example, one skilled in the chemical arts would utilize the following generic formula to define a phenyl ring substituted by the radical X:



This generic formula does not specify whether the bond of the substituent (X) is in the ortho, meta or para position. Rather, the generic formula covers all possible substitutions.

Likewise, the generic formula (II) as used in the claims covers various chemical structures which may differ with respect to the particular location of bonds. Furthermore, chemical formulae often contain functional elements, such as leaving group, oxidizable group, etc. For example, the term "linker" partly reflects a chemical moiety, namely that it is a chemical bridge between the resin and the scaffold attached to the linker and that a portion of the complex may be cleaved off of it later. The linker technology is known to one skilled in the art and is

discussed on pages 13 to 15 of the Specification. Specific types of suitable base-stable linker groups between the substrate and the solid phase support are shown in Table 1 of the specification on pages 16 to 17. Table 2 on page 18 to 20 provides additional examples of suitable acid stable linker groups. Accordingly, when the formulae are read in the light of the specification, and where the terms used and the generic nature and function of the elements are defined, one skilled in the art would recognize the types of compounds that are defined by the generic structures in the claims.

In addition, the reaction sequences and structural changes occurring during each of the reaction steps are properly reflected in the claims. For example, step (a) is defined as the reaction of compounds (II) and (III) in the presence of a palladium catalyst which proceeds via an exchange of the group S^1, wherein the functional group $P(H)(=O)\text{-}OA^1$ is introduced. This is known as a type of Heck-reaction and this reaction would be within the knowledge base of one skilled in combinatorial chemistry.

Further, in reaction step (b), the organic radical E^1 is modified to $(E^1)'$. The reaction types which may be selected by the skilled artisan need not be limited in advance to practice the claimed invention. The skilled artisan would determine which type of reaction would be conducted at this stage depending on the direction with which the chemist would like the reaction to proceed for the desired compounds to be formed. The selection of specific linkers, other functional groups and reaction types are generally part of the knowledge that a skilled chemist would rely upon when reading the claims in light of the specification.

With respect to reaction step (c), wherein the phosphorus-containing functional group is hydrolyzed, and likewise in the esterification step (d), which clearly modifies the phosphorus-containing group and not any other group, one skilled in the art would be able to

practice the claimed invention based on a reading of the specification and the general knowledge of chemist with respect to hydrolysis and esterification reactions. Further, reaction step (e), (f) and (g) are also clearly defined in the claims and further explained in the specification, such that one skilled in the art would understand the process steps as defined by all of the steps in the claimed process.

Further, looking to the specific formulae and structures used in the claims, it is asserted that the definition of terms such as "resin polymer, linker, Z, E^1 and S^1" are broad generic definitions but are not vague definition. With regard to the definition of Z, Z relates to the functional group of a linker which is transformed to Y by cleavage of compound (I) from the resin polymer in the last step of the process. The structure and function of Z is described to one skilled in the art in the specification on pages 13 to 14, bridging paragraph.

With regard to the definition of E^1, E^1 is defined functionally because the specific definition of E^1 is an independent selection made by one skilled in practicing the invention. The relationship between E^1 or $(E^1)'$ and R^1 is one of precursor and final product. The combinatorial process allows for broad variation of the moieties E^1 and R^1. The teaching of the invention is that modifications can be made on the solid-phase bound intermediates, and after the modifications, the final product can be cleaved from the resin. A claim limitation for very specific modifications would be unduly restrictive, and would not be required to convey the full scope of the claimed invention to one skilled in the art.

With regard to the definition of S, an important feature of the combinatorial process of the present invention is the palladium-catalyzed substitution (analogous to the Heck-reaction) of the group S^1 to form the phosphorus containing functional group at the heteroaromatic system. The Heck-reaction is well known and described in the specification on page 21, line 20 to page

22, line 25. At page 22, lines 6 to 14, the preferred definition for S^1 is also mentioned. Therefore, the term is used in a similar manner as common terms such as "esterification", "Michael-addition", "Diels-Alder-cycloaddition", and should be acceptable. Hence, the terms have a definite meaning to one skilled in the art when read in light of the specification.

With respect to the comment [2] on page 4 of the outstanding Office Action, that the claim language is **confusing at any** reader, Applicants respectfully assert that one skilled in the art would recognize that various derivatization reactions are possible, based on the reactions in steps (a) to (g). The specific definition of the type of reaction is an independent selection made by one skilled in the art in practicing the invention. The process is not limited to specific derivatization reactions and various derivatization reactions are possible. Further, the specific definition of an organic radical is an independent selection made by one skilled in the art in practicing the claimed invention. Accordingly, the process is not limited to specific derivatization reactions but would be based on decisions made by one skilled in the art.

A claim is definite if the scope of the subject matter embraced by a claim is clear and if the applicant has not otherwise indicated that he intends the claims to be of a different scope. In re Borkowski, 164 USPQ 642 (CCPA 1970). The "distinctly claim" requirement of 35 USC § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in light of the completely patent document. Standard Oil Co. v. American Cyanamid Co., 227 USPQ 293 (Fed. Cir. 1985). The test of definiteness is whether one skilled in the art would understand the scope of the claim when read in light of the specification. Morton Int. Inc. v. Cardinal Chem. Co., 28 USPQ2d 1190 (Fed. Cir. 1993). The degree of precision necessary is a function of the subject matter claimed. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986).

The purpose behind the combinatorial process is the creation of chemical libraries in an efficient manner. An important feature of the inventive process is not the specific modification reactions. Rather, it is the specificity of the resin-linker adduct and its broad practical use. As mentioned in the specification, the process is not limited to specific modification reactions or specific reaction conditions. The modification reactions are carried out under normal conditions known in the art for non-resin-bound reaction. Therefore, the definition of the type of modification reactions and substituents are not necessary for one skilled in the art to practice the invention as claimed.

For the foregoing reasons, Applicants respectfully maintain that the terms used in the claims convey a clear meaning to a practitioner in this art, when the terms are read in the context of the rest of the claim and in light of the specification. Moreover, Applicants urge that this language is precise in view of the nature of the claimed subject matter. Accordingly, these terms are precise and therefore not indefinite or vague and clearly described in the specification.

Therefore, Applicants assert that the processes as claimed in claims 2 to 9 and 16 are complete, the terms in the claims are not vague nor indefinite and clearly define the subject matter of the present invention based on the degree of precision necessary for the subject matter claimed and describe the metes and bounds of the invention to one skilled in the art, and fulfill the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of all of the rejections of the claims based on 35 U.S.C. § 112, second paragraph.

Claims 2 to 9 and 16 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Schwabacher et al ("Schwabacher')(Synthesis, 1992, pp. 1255 – 1260) in

combination with Boyd et al. ("Boyd")(Tetrahedron Letters, Vol. 37, No. 10, 1996, pp. 1647 – 1650). (Office Action, pages 5 to 10).

As neither of these publications taken alone, or in any fair combination, teach or suggest the inventive process, Applicants respectfully maintain that the claims are not obvious based on the combined teachings of Schwabacher and Boyd, and further that the references fail to constitute a *prima facia* case of obviousness, because there is no motivation or suggestion in either of the references to utilize the solid phase reactions and processes claimed in the present application.

Accordingly, Applicants respectfully request the withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) based on Schwabacher, in combination with Boyd, because Schwabacher does not teach the claimed invention for the reasons cited in the Office Action, and Boyd does not correct the deficiencies of the Schwabacher reference as Boyd does not teach solid phase synthesis for compounds where the phosphorus atom is bound to a heteraryl or aryl moiety. There is no motivation to combine these references because Boyd teaches a different reaction and does not indicate that the processes disclosed therein are equivalent to the solution reactions taught by Schwabacher. Further, this combination does not suggest the superior yields obtained by the inventive process. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

Schwabacher discloses the preparation of methyl esters of monoarylphosphinic acids which involves palladium catalyzed coupling of aryl iodides with methyl phosphinates in the presence of tertiary amines or propylene oxides. Both symmetrically and unsymmetrically substituted diarylphosphinate are disclosed.

Looking to the table on p. 1255 of Schwabacher, there is a summary of the yields of the

reactions based on the teachings of Schwabacher. These yields range from 23% to 80% for the disclosed reactions performed in solution. No further disclosure is provide indicating that the reactions can be performed by solid-phase synthesis, nor is there any suggestion that the yields could be improved by performing the Schwabacher reactions utilizing solid-phase synthesis.

The present invention teaches a combinatorial process using solid phase bound intermediates. Surprisingly, the palladium catalyzed Heck reaction process of the present invention works well with the solid phase bound starting materials. It would not have been expected that the reaction would work at all with the resin bound material. In principle, many side-reactions may occur on the resin. Surprisingly, the solid phase reaction (for example, the Heck reaction and subsequent derivatization reactions) work even better, i.e. result in better yields, when compared with similar reactions conducted in normal solutions. (See Specification, page 8, lines 3 to 14). For example, the yields reported by Schwabacher for the step of the Heck reaction recorded in the table on page 1255 are 23 to 80% of theory. In contrast, the processes of the present invention, up to and including the isolation of final products, produce compounds in higher yields at the end of each step, with yields in excess of 90% after cleavage of the final product from the resin.

These high yields are seen for other examples in the specification as well. Example 2 (Specification, page 37, line 16 to page 38, line 4) for the palladium-catalyzed reaction and Example 3 (Specification, page 38, lines 7 to 29) for the modification with an aldehyde and subsequent cleavage of the final product provide an example with a yield of 92%. Similarly, the combination of Example 2 with the reaction of Example 4 (Specification, page 39, lines 1 to 20) provide a further example with a combined yield of 94.6%.

These surprisingly good yields, together with the broad variability allowed for the

phosphorus-containing group and the substituents thereon in practicing the invention, demonstrate the non-obviousness of the invention over the prior art cited, as these processes would not have been expected to proceed so efficiently based on the prior art cited.

Boyd teaches the solid-phase synthesis for alkylphosphinic acids where the phosphorus atom is directly bound to a 1-aminoalkyl group. For example, discloses the synthesis of 1-aminophosphinic acids, whereby 9-amino-xanthen-3-yloxymethyl polystyrene is reacted with an aldehyde. A phosphate group is added to the substituent added on the amino group through the use of *bis*(trimethylsilyl)phosphinate. The final product, 1-aminophosphinic acid, is produced by cleavage of the amino group from the xanthene-3-yloxymethyl polystyrene, without further substitution on the phosphorus atom.

The reactions disclosed in Boyd differ from those of the present invention in that the reaction is not a Heck reaction. Further, the products disclosed in Boyd are not arylphosphinic acids that are comparable to the compounds of formula (I) of the present invention, where the phosphorus atom is bound to an aromatic or heteroaromatic ring. Alkyl radicals differ from aryl radicals considerably, and a functional group attached to an alkyl radical has a different reactivity when compared to the same functional group attached to an aryl radical. This follows indirectly from the different method of forming the C-P-bond. Boyd does not teach the effect or lack of interaction between the reagents used for the Heck reaction (arylhalide, phosphite, palladium catalyst) and the resin or the solid phase bound precursor under the conditions of the Heck reaction. It would not have been obvious to use the palladium catalyzed reaction with the solid phase synthesis and have an expectation of good yields.

Further, the reaction conditions applied by Boyd are not comparable. In particular, bis(trimethylsilyl)phosphonite is reacted to an alkylimino compound wherein the phosphorus

atom is added to the double bond in a Michael-type reaction. A palladium catalyst is not used. Therefore, the P-C-bond formed is a bond to a saturated carbon atom rather than an aromatic =CH-group as in the processes of the present invention.

Boyd mentions at page 1649, lines 1 to 3, that the resin bound aliphatic amines were labile and difficult to use. It is generally known in the art that hydrolysis is a concern with resin bound materials. On the other hand, the phosphinic acids are directly split off from the resin after their formation. The resin bound phosphinic acids are not further modified at the functional group or at other parts of the molecule. For instance, Boyd does not mention ester formation at the phosphorus group, nor that these esters might be subject to hydrolysis or other side-reactions on the resin. Accordingly, the preparation of the compounds (I) according to the present invention encompasses a much broader range of functional groups (including other oxidation states) which can be handled on the resin.

In addition, Boyd does not teach or suggest any other substitution on the phosphorus atom, nor is there any suggestion to bind a phosphorus atom directly to the solid support and provide further substitution or derivatization on the phosphorus atom. Therefore, one skilled in the art would not be motivated to combine the teachings of Boyd with the teachings of Schwabacher, because Schwabacher teaches chemical substitution directly on the phosphorus atom and Boyd does not.

Further, there is no suggestion or motivation in Schwabacher to utilize the solid phase support taught by Boyd, or any other solid phase support resin, for the reactions taught in Schwabacher. In fact, Schwabacher would lead one skilled in the art away from combining Schwabacher with Boyd. Schwabacher states on page 1257, column 1, third paragraph, "Attempts to use trimethylsilyl and tributylstannyl esters of hypophosphorus acid led to only

trace quantities of the desired phosphinates. Water scavengers such as *bis*(trimethylsilyl)acetamide or molecular sieves also failed to improve the yields in reactions of methyl phosphinate." Boyd teaches the use of *bis*(trimethylsilyl) phosphinate in the reaction forming 1-aminophosphinic acid. Therefore, one skilled in the art would not have been motivated, nor would one skilled in the art have a reasonable expectation of success, based on Schwabacher in combination with Boyd.

Further, there is no suggestion or motivation in Boyd for one skilled in the art to combine the teachings in Boyd with Schwabacher and practice the invention of this application. Boyd does not teach the solid phase synthesis of compounds whereby the phosphorus atom is bound to a heteroaryl or aryl moiety as in the present invention.

Reconsideration of the Section 103 rejection is respectfully requested with the following in mind. First, it is well established in patent law that in order to show a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Second, there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the primary reference in the manner suggested by the Examiner. In re Laskowski, 12 USPQ 2d 1397, 1399 (Fed. Cir. 1989). Third, "obvious to try" is not the standard under 35 U.S.C. § 103. In re Fine, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988). Further, as stated by the Court in In re Fritch, 23 USPQ 2d 1780, 1783-1784 (Fed. Cir. 1992):

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.

For a proper Section 103 rejection, the reference must provide some suggestion, which would motivate the skilled artisan to modify the reference teachings as suggested by the Examiner. In re Fitch, 23 U.S.P.Q. 2d 1730, 1783-84 (Fed. Cir. 1992). The references upon which the Examiner bases the Section 103 rejections do not motivate or suggest the processes of the present invention.

Accordingly, the references relied upon in the Office Action fail to provide the necessary incentive or motivation for modifying the references in the manner which would produce the invention as claimed because the references do not teach or suggest the combinatorial processes of the present invention. A *prima facie* case of obviousness cannot be established by picking an choosing from the isolated disclosure of the references and modifying the references without any suggestion to make the modification. It is impermissible for the motivation to modify the references to come from a reading of the disclosure of the present application. Therefore, the cited references do not render the claimed invention obvious.

Thus, in view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) based on Schwabacher in combination with Boyd is respectfully requested.

Claims 2 to 9 and 16 were rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not provide reasonable enablement for a method for the preparation of all phosphorus compound derivatives that are potentially suggested by the claims, using all linkers, all reactants with all potential types of functional group substitution patterns on each of those reactants, on all resins as means to effectuate the synthesis of desired products, and it is alleged that one skilled in the art could not practice the claimed invention without undue experimentation. (Office Action, pages 10 to 13).

Applicants respectfully maintain that the specification fully complies with the first

paragraph of Section 112, and that the specification in combination with the knowledge of one skilled in the art fully enables one to practice the invention as claimed without the need to perform undue experimentation.

The present invention is directed to combinatorial chemistry processes that have broad applicability. Part of the invention rests on the observation that the Heck reaction can be performed by solid phase synthesis on resins with surprisingly high yields and effectiveness. The Heck reaction is a well defined reaction that would be known to one skilled in the art, whereby the other reactions in the overall process of the present invention involve synthesis steps that are more or less independent of the Heck reaction. These other reaction types would be selected by the skilled artisan based on the general knowledge in chemistry in practicing the claimed process. Since the claimed processes involve multi-step syntheses which include a the Heck reaction, with the requirements for the selected phosphorus-containing substrate and its associated chemistry, the variability in the claimed processes are dependent on the selections of the other reaction types by one skilled in the art, and such selection would be based on either a reading of the specification and claims of the present invention or be based on the general chemical knowledge of one skilled in the art.

Another aspect of the invention is based on the fact that the resin bound adducts of arylphosphinates, and derivatives thereof, are surprisingly stable. The specific examples of the specification provide guidance in practicing the processes of the claimed invention and can be easily modified by one skilled in the art. For example, the reactions can be modified at the functional group or at other parts of the molecule without serious loss in yield or serious interaction with the resin. Accordingly, these modifications clearly fall within the overall concept of the combinatorial synthesis of the present invention and the selection of particular

modifications would be based on the artisan's general knowledge of chemistry.

The specific working examples in the specification, which employed specific linker and reactions, provide guidance in practicing the claimed invention, and also demonstrate the advantageous potential of the example and like processes. The specification also provides guidance in determining the effectiveness of a given selection of reaction type. For example, one skilled in the art could modify the specific examples of the specification and compare the yields with those of the example to determine the effectiveness of the selected modification relative to the example.

As acknowledged in the Office Action on page 11, the specification does enable processes as described in Schemes 1 and 2 and the Examples. The Reaction Schemes and Examples provide both general methods whereby various substituents can be replaced, as well as providing specific examples of various compounds formed by specific reactions. They include starting compounds and potential intermediates (including proposed substituents), reaction conditions, examples of various linker compounds and the preparation of the resin-linker compounds, and analytical methods for the identification of the compounds produced in the given examples. The breadth of the possible substituent and reaction types identified in Schemes 1 and 2 alone clearly demonstrate to one skilled in the art that the claimed processes can be applied to a wide range of chemical reactions known in the art.

These Schemes and Examples could be easily modified by one skilled in the art. Even if a chemist were to choose a non-optimal reaction type for the modification, for example in the formation of the compound of formula (IV) obtained in step (a), the chemist could still make use of step (a) of the process. The conditions of the additional reactions would then be adapted in a conventional manner using common chemical methods. The linker systems used or the problems

of cross-reactivity of multifunctional molecules are widely known in the art.

The Office Action alleges that the person skilled in the art could not practice the claimed invention without undue experimentation, although the steps (b) to (f) and even (g) follow known chemical methods within the general knowledge of the skilled chemist. The numerous reaction schemes and working examples of the application could easily be modified by one skilled in the art without the need for undue experimentation. Further, it is not necessary that the specification recite every potential chemical reaction that could be used in practicing the claimed process if these reaction as known in the art. As discussed below, the specification need not disclose, and best omits, that which is well known in the art.

Thus, the full scope of the pending claims are supported by the specification in combination with the knowledge of the art and Applicants urge that the specification adequately teaches how to make and use the full scope of the invention as claimed.

The Examiner's attention is respectively invited to some case law under the first paragraph of Section 112. First, it is a well known principle that claims must be read in light of the specification. See In re Marosi, 710 F2d 799, 218 USPQ 289 (Fed. Cir. 1983). The first paragraph of Section 112 requires nothing more than objective enablement. How this is accomplished is of no importance. In re Marzocchi, 169 U.S.P.Q. 367 (CCPA 1971). Second, it has been determined that the claims need not be limited to preferred embodiments in the specification. It is improper, according to In re Goffe, 191 U.S.P.Q. 429,431 (CCPA 1976), to limit the claims of an application to the specific examples in the specification under the guise of lack of enablement:

> To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials...would not serve the constitutional purpose of promoting progress in the useful arts.

Third, it is urged that the subject matter in the claims is not broader than the enabling disclosure. Applicants respectfully submit that the claims are more than adequately supported by the specification. There is no particular number of examples which makes specific claim language adequate or enabled. Indeed, enablement is not even related to the number of examples in the specification. In In re Borkowski, 164 USPQ 642,646 (CCPA 1972), the court stated: There is no magical relation between the number of representative examples and the breadth of the claims... the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated'.

Moreover, "the laws does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC §112". Staehelin v. Secher, 24 USPQ2d 1513, 1516 (Bd.Pat.App.&Int. 1992) Indeed, a specification need not disclose--and best omits--that which is well known in the art. In re Buchner, 929 F2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

In addition, it is respectfully urged that enablement is not precluded even if some experimentation is necessary, provided it is not unduly extensive. Hybridtech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). A disclosure is enabling even if considerable amounts of experimentation is involved, if that experimentation is routine. Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986). In Ex parte Forman, the Board described what constitutes undue experimentation as follows:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed to enable the determination of how to practice a

> desired embodiment of the invention claimed. The factors considered have been summarized as the quantity of experimentation necessary, the amount of direction and guidance presented, the presence or absence of working examples, the nature of the invention, the relative skill of those in the art, the predictability and unpredictability of the art and the breadth of the claims.

It is respectfully asserted that any experimentation required by the present application is routine for the skilled chemist relating to the selection of a given reaction type, and sufficient guidance and direction for that experimentation is provided in the specification.

Thus, in view of the foregoing, it is respectfully submitted that the teachings in the application in combination with the knowledge in the art fully enable one skilled in the art to make and use the claimed invention without undue experimentation. Accordingly, reconsideration and withdrawal of the Section 112, first paragraph rejections are respectfully requested.

In view of these remarks, it is respectfully requested that all of the rejections of this application be reconsidered and withdrawn and that this application is in condition for allowance. Reconsideration of this application, consideration of new claim 16 and prompt issuance of a Notice of Allowance, with claims 2 to 9, and 16 are earnestly solicited. If there are any minor issues which remain an impediment to allowance, the Examiner is respectfully requested to contact the undersigned by telephone.

Respectfully submitted,

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